REMARKS

Claims 2-5 and 8-16 are currently pending in the application. Claims 3-5 and 8-14 are withdrawn from consideration. Claim 15 is in independent form.

Applicants express their appreciation to the Examiner for the courtesies extended during the personal interview with Applicant's representative, Kenneth I. Kohn on August 2, 2007.

I. Applicants have overcome the rejection of claims 2, 15, and 16 under 35 U.S.C. §112, first paragraph.

Claims 2, 15, and 16 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement because of limitations that are new concepts because they do not have literal support in the as-filed specification by way of generic disclosure, nor are there specific examples. Specifically, the Office Action holds that the limitation "the products consisting essentially of the secretions from the stem cells" has no support in the as-filed specification as the generic disclosure relates to the potential benefits of the stem cells in combinations with their secretions but not to the secretions alone as a sole therapeutic agent. Reconsideration of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claim 15 has been amended to more clearly define the invention. Support in the specification for each step of the method is detailed as follows. Applicants stress that adequate support for each of the steps of the method is present in the specification. There is no law that states that the claims must be supported only in the "example" section of the specification directed to stem cell transplantation in dogs. The specification as a whole is enabling.

"The claims of a patent are always to be read or interpreted in the light of its specification." *Schriber-Schroth Co. v. Cleveland Trust Co.*, 311 U.S. 211, 217; 61 S. Ct. 235, 238 (1940). "[T]he real invention is to be found in the specification and drawings, and that the language of the claims is to be construed in the light of what is there shown and described." *Burroughs Adding Mach. Co. v. Felt &Tarrant Mfg. Co.*, 243 F. 861, 868 (1917). Note there is no requirement to interpret claims based on a particular ***section*** of the specification.

"That a specification describes only one embodiment does not require that each claim be limited to that one embodiment." *Sri International v. Matsushita Electric Corporation of America*, 775 F.2d 1107, 1121 (CAFC 1985). "[A]s a general rule ***claims of a patent are not limited*** to the preferred embodiment, or ***to the examples listed within the patent specification***." *Dow Chemical Company v. United States*, 226 F.3d 1334, 1342 (2000), emphasis added. Thus, while Applicants' examples are directed to stem cell transplantation in dogs, there is no reason that the claims must be also only directed to those examples. The specification as a whole is fair game for the creation of claims. Therefore, Applicants have utilized the entire specification in showing support for claim 15 in the chart below.

administering stem cell products consisting essentially of secretions from mesenchymal stem cells	- "...the present invention provides a method and composition for improving and/or restoring cardiac function by administering a composition..." p. 4, lines 7-9 - "The purpose of the present invention is to utilize stem cells, supernatant from stem cells, the secretions resulting from the interaction of stem cells and other cells (e.g., stem cell products), or compounds that increase the amount of secretions present at a site, for treating heart failure." p. 4, lines 23-26 - "The term 'cell therapy' as used herein is meant to include but is not limited to, the administration of stem cells and their products as defined above." p. 6, lines 26-28 - "... bone marrow stromal cells can be employed as cellular factories for producing and secreting trophic, growth, and angiogenic factors." p. 7, lines 20-22 - "Alternatively, cardiac function can be increased by administering stem cell factor/products to a location in need of such treatment." p. 8, lines 17-19 - "Additionally, the stem cells or stem cell factors/products can be also responsible for the release of various substances such as trophic factors, which, for example, induce angiogenesis (increase the number of blood vessels) in order to increase cardiac function and/or treat heart failure." p. 8, lines 20-23 - "The method includes the step of administering, to a patient, stem cells or stem cell factor/products." p. 8,

	lines 29-30 - "The stem cells are merely harvested, expanded if necessary, and administered." p. 8, line 31 – p. 9, line 1 - "The present invention simplifies the entire procedure by only requiring the administration of stem cells without any genetic engineering or additional compounds." p. 9, lines 7-9 - "The stem cells or products thereof can be administered at the specific location of injury. Alternatively, ... the stem cells and stem cell products can be administered intravenously and/or intracoronary. ...the stem cell products can affect cardiac function regardless of the location of administration. This enables the stem cells or stem cell products to be administered at any location in the patient." p. 9, lines 11-21 - "The administration can be subcutaneously, parenterally including intravenous, intraarterially, and intranasally as well as intrathecally and infusion techniques." p. 9, lines 25-27 - "The dosage of the mesenchymal stem cells varies ... in the case of parenteral administration, it is customary to administer from about 0.01 to about 5 million cells per kilogram of recipient body weight. ... The mesenchymal stem cells can be administered by a route that is suitable for the tissue, organ, or cells to be transplanted. They can be administered systemically,

	... can be administered via subcutaneous implantation of cells or by injection into connective tissue, e.g., muscle." p. 12, lines 20-31 - "The therapy of the invention can be provided by several routes of administration, including the following ... intracardiac muscle injection." p. 14, lines 15-16 - "In the media, expression of HIF-1α was significantly higher after one hour exposure to HX." p. 23, lines 26-27 - "Based upon the above findings, it can be concluded that hypoxia preconditioned BMSC media represents a potential drug for treatment of the failing heart...." p. 24, lines 19-21
isolating the mesenchymal stem cells from harvested marrow	- "...'stem cells' refers to human marrow stromal cells ... [which] are found in the bone marrow." p. 5, lines 3-5 - "...bone marrow is a complex tissue comprised of hematopoietic stem cells, ... mesenchymal stem cells ...." p. 5, lines 14-16 - "Recent evidence indicates that these cells, called pluripotent stromal stem cells or mesenchymal stem cells, have the ability to generate into several different types of cell lines ... upon activation." p. 5, lines 25-29 - "... bone marrow stromal cells can be employed as cellular factories for producing and secreting trophic, growth, and angiogenic factors." p. 7, lines 20-22 - "The stem cells are merely harvested, expanded if

	necessary, and administered." p. 8, line 31 – p. 9, line 1 - "The human mesenchymal stem cells can be obtained from a number of different sources ... from aspirated marrow obtained from normal donors and oncology patients who have marrow harvested for future bone marrow transplantation." p. 10, lines 1-6 - "... the critical step involved in the isolation processes was the use of a specially prepared medium that contained agents that allowed for not only mesenchymal stem cell growth without differentiation, but also for the direct adherence of only the mesenchymal stem cells to the plastic or glass surface area of the culture dish." p. 10, lines 9-13 - "When plugs of cancellous bone marrow were utilized ...." p. 10, line 25 - "The single cell suspension ... was then subsequently plated in 100 mm dishes for the purpose of selectively separating and/or isolating the mesenchymal stem cells from the remaining cells found in the solution." p. 11, lines 6-10 - "When aspirated marrow was utilized as the source of the human mesenchymal stem cells...." p. 11, lines 12-13 - "The low-density platelet fraction was then plated in the Petri dish for selective separation based upon cell adherence." p. 11, lines 22-24 - "The marrow cells obtained from either the cancellous

	bone or iliac aspirate ... were grown in complete medium and allowed to adhere to the surface of the Petri dishes for one to seven days according to the conditions set forth below." p. 11, lines 26-29 - "...mesenchymal stem cells can be isolated, preferably from bone marrow, purified, and expanded in culture...." p. 13, lines 9-11
growing the mesenchymal stem cells without differentiation in medium	- "The stem cells have not been previously differentiated or otherwise treated. The stem cells are merely harvested, expanded if necessary, and administered." p. 8, line 30 – p. 9, line 1 - "The present invention simplifies the entire procedure by only requiring the administration of stem cells without any genetic engineering or additional compounds." p. 9, lines 7-9 - "... the critical step involved in the isolation processes was the use of a specially prepared medium that contained agents that allowed for not only mesenchymal stem cell growth without differentiation, but also for the direct adherence of only the mesenchymal stem cells to the plastic or glass surface area of the culture dish." p. 10, lines 9-13
enriching the medium containing the mesenchymal stem cells	- "The terms "enrich" or "enrichment" as used herein are meant to include, but are not limited to, a process of making rich or richer by the addition or increase of some desirable quality or quantity of substance." p. 6, lines 12-14 - "Optionally, the medium can be enriched by exposing

	the media to hypoxia. The enrichment enables the stem cells and stem cell products to be used as a treatment." p. 10, lines 18-20 - "Exposure of BMSC to one hour of HX resulted in a six-fold increase in STAT-3 expression compared to BMSC exposed to NX. p. 18, lines 7-9 - "HX was produced by placing BMSC in an airtight incubator..." p. 23, lines 3-4
separating the mesenchymal stem cells from a supernatant, the supernatant containing products consisting essentially of secretions from the mesenchymal stem cells	- "The purpose of the present invention is to utilize stem cells, supernatant from stem cells, the secretions resulting from the interaction of stem cells and other cells (e.g., stem cell products), or compounds that increase the amount of secretions present at a site, for treating heart failure." p. 4, lines 23-26 - "BMSC were harvested after one hour of exposure to HX or NX. The media left after harvesting of BMSC was used for another set of experiments." p. 23, lines 5-7 - see also arguments below under §112, first paragraph
improving cardiac function	- "The method of the present invention promotes an improved outcome from cardiac injury by augmenting or causing the regeneration of cardiac muscle cells." p. 4, lines 29-31 - "The stem cells operate to increase cardiac function and/or treat heart failure by differentiating into functional cardiac muscle cells, thereby treating the injury." p. 7, lines 1-3 - "The solution to this problem [death of heart muscle

	cells] is to enrich and/or repopulate the myocardium with new functional cardiac cells that take the place of lost cells or provide additional reinforcement of the currently functioning cardiac cell, thereby improving the pumping function of the failing heart." p. 7, lines 5-11 - "The present invention treats heart failure and improves and/or restores cardiac function. Cardiac function is increased by enriching and/or repopulating cardiac cells, particularly contractile units, through transplanted stem cells that differentiate into cardiac cells. Alternatively, cardiac function can be increased by administering stem cell factor/products to a location in need of such treatment. Thus, the increase of contractile units increases the function of the heart. Additionally, the stem cells or stem cell factors/products can be also responsible for the release of various substances such as trophic factors, which, for example, induce angiogenesis (increase the number of blood vessels) in order to increase cardiac function and/or treat heart failure. Therefore, the stem cells operate to increase cardiac function and/or treat heart failure through various mechanisms other than just differentiating into functional cardiac muscle cells." p. 8, lines 14-26 - "The present invention provides a method and composition for treating heart failure." p. 8, lines 28-29 - "...the stem cell products can affect cardiac function regardless of the location of administration." p. 9, lines

	18-19 - "... regional function of the failing left ventricle improves dramatically one month after transplantation of autologous bone marrow stem cells into that region of the ventricle...." p. 13, lines 26-28 - "Repopulation of the myocardium with stem cells that differentiate into contractile units that contribute to the overall function of the failing heart, therefore, is novel and goes to the center of the problem." p. 16, lines 2-4 - "Bone marrow stem cell (BMSC) transplantation has been shown to regenerate infracted myocardium (M) and improve LV function." p. 17, lines 20-21 - "Based upon the above findings, it can be concluded that hypoxia preconditioned BMSC media represents a potential drug for treatment of the failing heart...." p. 24, lines 19-21

With respect to the limitation "the products consisting essentially of the secretions from the stem cells," the Office Action refers to the paragraph at lines 23-31 on page 4 of the specification wherein it is stated that "the purpose of the present invention is to utilize stem cells, supernatant from stem cells, the secretions resulting from the interaction of stem cells and other cells (e.g., stem cell products), *or* compounds that increase the amount of secretions present at a site, for treating heart failure" (emphasis added). Applicants point out the use of alternative language in this paragraph, italicized above, meaning that *any one* of stem cell, supernatant, secretions, or compounds increasing secretions can be administered. There is no requirement that any of these components be used together.

The specification clearly discloses that "the stem cells *or products thereof* can be administered at the specific location of the injury." Specification, page 9, lines 11-12, emphasis added. There is no requirement that the stem cells and the stem cell products must be administered together, as they can be administered separately or together based on lines 11-12 of page 9. The statement of the Office Action referring to page 9, lines 15-18 of the specification that the stem cells can produce products at the site of administration is referring to the case when stem cells and stem cell products are administered together. Thus, stem cells alone can be administered that will produce secretions *in vivo*; however, as the paragraph also states, these secretions can be administered by themselves without the stem cells. Therefore, the specification is fully supported for the limitation of "the products consisting essentially of the secretions from the stem cells."

Furthermore, there is detailed support for the method step of "administration". There are numerous instances in the specification where administration is mentioned as well as different types of administration, several as shown in the chart above. It would be absurd to hold that there is no support for "administration" of the stem cell products. In the detailed description alone, "administration" or a variant thereof can be found 27 different times. It is hard to understand how Applicants have shown that cardiac function has improved, especially in the examples involving experiments on dogs, if no administration of stem cells or stem cell products has occurred.

Also, there is no requirement that the "stem cell products" be fully characterized such that every factor that could possibly be produced by a stem cell is listed.

> "[N]othing in the law requires the courts to deny a patent to the inventor of a new and useful product merely because laboratory technique has not advanced to a point where the chemical structure can be recognized and described. All that is necessary is that the patentee make as full disclosure

> as he reasonably can and that he describe the product with sufficient particularity that it can be identified...." *Benger Laboratories Limited v. R.K. Laros Company v. Armour And Company*, 209 F. Supp. 639, 642 (1962).

One skilled in the art would know what a "stem cell product" is. Furthermore, one skilled in the art would be able to discern which factors are being produced by the stem cells depending upon the conditions that the stem cells are in at any given time. For example, Applicants show that HIF-1α was included as one of the "stem cell products" found in the supernatant. However, this was just one factor that Applicants tested for. Applicants disclose in the specification various factors that *could* be produced by the stem cells. This is all that is required by the courts. It is sufficient to call these factors as a group the generic term "stem cell products".

The Office Action further holds that the limitation "separating the stem cells from a supernatant, the supernatant containing the products consisting essentially of secretions from the stem cells; and administering the products consisting essentially of the secretions from the stem cells" has no support in the as-filed specification. With respect to Applicants' previous argument that one of skill in the art would have known how to obtain and to separate a supernatant from the stem cells, the Office Action holds that the rejection is a matter of written description, not a question of what one of skill in the art would or would not have known.

With respect to this limitation, Applicants respectfully point out that there is no requirement to include in the specification what is already known in the art.

"[A] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

One utilizing the teachings of this application would be able to perform a separation of the supernatant, as separating cells and cell products from supernatant is a basic skill that one skilled in the art would be able to perform. Such separation processes include, for example, centrifugation. There is no reason why Applicants should be required to explain how to perform a simple laboratory technique, when, as stated above, the courts have concluded that such information is preferably left out of the application.

Further, as recited in the above chart, the specification does refer to the supernatant as being able to be administered to a patient: "The purpose of the present invention is to utilize stem cells, *supernatant from stem cells, the secretions resulting from the interaction of stem cells and other cells (e.g., stem cell products)*, or compounds that increase the amount of secretions present at a site, for treating heart failure." (p. 4, lines 23-26, emphasis added) Also, the examples disclose using the supernatant: "BMSC were harvested after one hour of exposure to HX or NX. The *media left after harvesting of BMSC* was used for another set of experiments." (p. 23, lines 5-7, emphasis added) While the supernatant itself is disclosed in the specification, as demonstrated above from case law, there is no need to include the actual process of separating stem cells from the supernatant, as this is a readily known process to one skilled in the art. Therefore, the limitation of "separating the stem cells from a supernatant" is fully supported by the specification.

Also, there is sufficient precedent for reciting a step of "improving cardiac function". There are several patents that recite this language, specifically stating "a method for improving cardiac function." See U.S. Patent Nos. 6,155,968 and 6,852,076. Applicants have herein sufficiently provided support for this step throughout the specification as shown in the table above.

As each step of the claims is fully supported by the specification and the Office Action's specific issues with the language of the claims have been addressed herein,

reconsideration of the rejection under 35 U.S.C. §112 to claims 2, 15, and 16 is respectfully requested.

II. Applicants have overcome the rejection of claims 2, 15, and 16 under 35 U.S.C. § 102(b) as being anticipated by Pierpaolli, et al.

Claims 2, 15, and 16 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Pierpaolli, et al. Specifically, the Office Action holds that Pierpaolli, et al. discloses a method comprising the steps of a) isolating stem cells from harvested marrow, b) growing the stem cells without differentiation in medium or storing cells in the medium, c) enriching the medium containing the stem cells under hypoxia or storing cells in a closed vessel in a refrigerator, d) separating the stem cells from a supernatant, the supernatant containing "products consisting essentially of secretions from the stem cell" that would be "MRF", and e) administering the MRF intravenously. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by Pierpaolli, et al., as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

Pierpaolli, et al. teaches the administration of marrow regulating factors (MRF) obtained by suspending bone marrow in supernatant and then centrifuging the supernatant, passing the supernatant over a filter, and collecting the material that did not pass through the filter to administer to mice (p. 219-221). This reference is concerned with immune system reconstitution, and does not teach anything about improving cardiac function.

First, with respect to the rejection under §112 above, Applicants point out that from this reference, it is clear that separating a material from a supernatant is known in the art. Second, with respect to the present §102 rejection, Pierpaolli does not disclose critical

steps of independent claim 15. There is no disclosure whatsoever of growing stem cells without differentiation in medium, enriching the medium containing the stem cells, separating the stem cells from the supernatant wherein the supernatant contains products consisting essentially of secretions from the stem cells, and administering the products consisting essentially of the secretions from the stem cells. Pierpaolli, et al. does not use the medium of the present invention, which is specially prepared and contains "agents that allowed for not only mesenchymal stem cell growth without differentiation, but also for the direct adherence of only the mesenchymal stem cells to the plastic or glass surface area of the culture dish. By producing a medium that allowed for the selective attachment of the desired mesenchymal stem sells that were present in the marrow samples in very minute amounts, it was possible to separate the mesenchymal stem cells from other cells ... present in the bone marrow." Specification, page 10, lines 10-18. Because Pierpaolli, et al. is not using such a medium, the same products of the bone marrow will not be collected. Pierpaolli, et al. does not enrich its supernatant. Further, Pierpaolli, et al. does not teach administering the supernatant itself, but rather the filtered product separated from the supernatant. The supernatant is not used at all. According to the presently pending independent claim, Applicants separate out the stem cells, and administer the supernatant which contains the secreted stem cell products. Also, Pierpaolli, et al. is not administering only secretions of stem cells, but rather an ultrafiltration fraction of MW > 100,000 MRF.

Therefore, since the Pierpaolli, et al. reference does not disclose growing stem cells without differentiation in medium, enriching the medium containing the stem cells, separating the stem cells from the supernatant wherein the supernatant contains products consisting essentially of secretions from the stem cells, and administering the products consisting essentially of the secretions from the stem cells as set forth in the presently pending independent claim, the claim is patentable over the Pierpaolli, et al. reference and reconsideration of the rejection is respectfully requested.

Claims 2, 15, and 16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 7,097,832 to Kornowski, et al (hereinafter the '832 patent). Specifically, the Office Action holds that the '832 patent discloses and/or suggests a method of improving cardiac function wherein the method comprises steps of culturing bone marrow stem cells under hypoxia conditions for enrichment in the secretions from the stem cells and administering bone marrow stem cells and the bone marrow secretion products. The '832 patent discloses that the bone marrow secreted factors are necessary to promote new blood vessel growth and to restore function of ischemic heart and it also suggests administration of the bone marrow cell secretions. Therefore, the Office Action holds that it would have been obvious to administer the bone marrow stem cell secretions to the ischemic heart with a reasonable expectation of success. Reconsideration of the rejection under 35 U.S.C. §103(a), as being unpatentable over the '832 patent is respectfully requested.

The '832 patent discloses a method of treating cardiac or myocardial conditions by administering autologous bone marrow. The marrow can be exposed to hypoxia to activate the transcription factor HIF-1. The marrow is injected into a patient and there it secretes angiogenic factors. There is no disclosure or suggestion of performing the method disclosed by Applicants in presently pending independent claim 15. It is already known in the art, as Applicants explain in the background section of the specification, that marrow itself can be injected into the myocardium and stromal cells in the marrow can show growth potential. No one, however, has shown or suggested that secretions from stem cells can be separated and administered alone without administering the actual stem cells as well, i.e. only administering the supernatant separated from the stem cells, which themselves have been specifically separated from the bone marrow. There cannot be a reasonable expectation of success from the disclosure of the '832 patent based on

administering bone marrow in its entirety when no experiments have been performed administering only the secretions of stem cells.

Since neither the '832 patent alone or in combination with knowledge in the art suggests the currently claimed invention, it is consequently respectfully submitted that the claims are clearly patentable over the combination, even if the combination were to be applied in opposition to applicable law, and reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, and the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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